Prevention of Environmentally Related Diseases

The National Institute of Environmental Health Sciences is dedicated to reducing human diseases through a multidisciplinary approach focused on prevention of environmentally related illnesses. A central question is how best to focus our research and other activities to have the greatest impact on human health. Current research activities at the NIEHS are directed toward these goals, but improvements in certain areas, together with an enhanced emphasis on environmentally relevant diseases, can greatly expedite the achievement of our public health mission.

A successful program for prevention of environmentally related diseases should have three components that must be integrative and interactive: 1) identification of environmental hazards, 2) elucidation of mechanisms of environmental agents and environmentally related diseases, and 3) development and refinement of risk assessment methodologies.

The National Toxicology Program has unquestionably the world's premier program for carcinogen identification. The NTP bioassay should continue to be the cornerstone of the NIEHS program of prevention of environmentally related diseases by identifying agents that have the potential to cause human cancer and other chronic disorders. A question exists, however, about whether the program identifies the major environmental causes of human cancers. It is imperative to ask whether the strategies used to select chemicals for NTP testing are the most relevant and have the largest possible impact on the identification of causes of human cancer and other environmentally related diseases. It would be interesting (if it were possible) to estimate the total number of potentially preventable human cancers attributable to the carcinogens so far identified by the NTP; the number could be a very small percentage of all cancers. Therefore, new principles should be adopted to improve the selection of chemicals and testing procedures. Some examples of these principles are as follows.

• Exploit what is known. We should take advantage of the advances in our knowledge about mechanisms of environmentally related diseases that may allow more chemicals to be evaluated and predicted (tested) by alternative means. For example, the role of mutagenesis in carcinogenesis is clearly established; thus, there is little need to continue to study mutagens in two-year carcinogenesis bioassays for carcinogen identification. Even though some chemical mutagens are inactive in the standard bioassay, these are potentially carcinogenic in other contexts, and perhaps mutagens per se should receive greater attention from regulatory agencies. Internationally accepted procedures for mutagen evaluation *in vitro* and *in vivo* should be more uniformly and widely adopted, and chemicals that are clearly positive should be considered reasonably anticipated to be carcinogenic to humans. This would allow evaluation of a larger number of chemicals by alternative, short-term tests. Alternative approaches to dose–response relationships for risk assessment could be based on mutagenic or preneoplastic endpoints.

In addition, evaluation of chemicals by structure–activity relationships is another alternative to the two-year bioassay (*1*). For those classes of chemicals where our knowledge is limited, bioassays should be performed to test hypotheses related to structure–activity relationships. Furthermore, where our knowledge is substantial, bioassays are not necessary and certain chemicals or classes of chemicals should be assumed to be carcinogenic to humans (e.g., nitrosamines, anthraquinones, and benzidine congeners) (*2*). The recent success of Tennant and co-workers (*1*) in predicting the outcomes of rodent carcinogenicity tests demonstrates that alternative approaches to carcinogen identification are feasible. Although this approach is not possible with all chemicals, there are certain chemicals and classes of chemicals for which predictive toxicology is possible based on knowledge of mechanisms of action. Additional alternatives to the two-year bioassay include short- and mid-term *in vivo* assays (*3*), transgenic animals (*4*), alternative species including aquatic animals (*5*), and cell culture models (*6*). These are valuable for evaluation of chemicals for noncancer as well as carcinogenic effects, for identifying possible mechanisms, and for establishing priorities in the selection of chemicals that should be tested in two-year bioassays. Another practical consideration would be simply to reduce the size of the two-year studies by using only male rats and female mice and to adopt modified protocols (*2,7*). This has been shown, in a retrospective evaluation of standard two-species, both-sex studies, to have "correctly" identified 96% of the "positive" and "negative" studies (*2,7,8*). Theoretically, this would allow evaluation of nearly twice as many chemicals with the same resources. Further, expanded bioassays of transgenerational carcinogenesis may be warranted (*9*).

The NTP bioassay has identified several potent rodent carcinogens (*2,10*). It is important to identify human cohorts exposed to these chemicals for epidemiological studies to determine if there is evidence of their carcinogenicity in humans.

• Use multidisciplinary approaches to focus on important causes of human cancers based on epidemiological clues. Hopes for prevention of human cancer are based on the high percentage of cancers that are environmentally related. Yet these hopes are not being realized. Industrial chemicals are likely to contribute to fewer human cancers than several other causes, including tobacco, diet, alcoholic beverages, hormones, UV light, and viruses. These also represent preventable causes of human cancer, and a program of prevention should focus on all environmental agents. Of course, human cancers probably result from interactions between multiple etiological factors. Diet appears to represent a major environmental determinant of human cancer, but the scientific knowledge of what dietary factors are important and how they influence carcinogenesis is still rudimentary (*11,12*). The NTP/NIEHS could make a major impact in this important area of cancer prevention. The role of diet in the NTP bioassay should continue to be addressed (*13*). Evaluation of dietary factors for carcinogenic, co-carcinogenic, and anti-carcinogenic activity, coupled with studies of mechanisms and epidemiology, would have a significant scientific and public health impact. For example, there is a growing body of evidence that consumption of fresh fruit and vegetables is associated with a decreased risk of cancer, particularly for the digestive tract and hormone-related cancers (*14*). Advances in molecular biology of cancer could rapidly improve our ability to identify and understand dietary/nutritional factors in carcinogenesis.

Another area that could benefit considerably from multidisciplinary approaches is the role of hormones in cancer (*15*). Our new initiative in receptor-mediated pathobiology may provide an example of how to identify environmental estrogens using an alternative approach (*16*).

The incidence of non-Hodgkin's lymphoma is increasing faster than any other cancer in the United States (*17*). Increases in this cancer in agricultural communities suggest a pesticide, herbicide, or other agricultural exposure as a causative factor (*18–20*). The environmental cause(s) for this cancer should be better established. Again, interactive studies using animal models combined with epidemiological investigations and molecular biology research should be pursued.

• Develop models for important human cancers. Relatively few carcinogens have been identified for important human cancers, including breast, ovarian, prostatic, and colon cancers (*15*). Development of better animal and cell culture models for these cancers could lead to establishment of new tests for environmental causes of these cancers.

• Develop and define models for human predisposition and suscepti-

bility to cancer. The current regulatory and public health stance is to use the most sensitive strain of animal to predict possible responses of the most susceptible human subpopulation to a carcinogen, which is a nonscientific approach to quantitative risk assessment. In the past, the lack of scientific knowledge prevented quantitative analyses of genetic predisposition to carcinogenic exposures. This is not as true today. Our understanding of the genetic basis for predispositions is rapidly expanding and should be a major area of study for risk assessment. New mechanistic studies also allow for the development of better animal models for quantitative assessment of carcinogenic risks. Transgenic mice and genetically selected rodents that recapitulate human predispositions to certain cancers and other environmentally related diseases should be developed. Increased efforts should be made to clone and characterize tumor susceptibility genes in mice, such as the *Hcs* and *Pas* genes, which are major determinants of susceptibility to liver and lung carcinogenesis in mice (*21,22*). This would aid in the evaluation of responses at these common cancer sites in the NTP bioassay as well as possibly representing new cancer susceptibility genes for liver and lung cancer in humans. The generation of transgenic mouse models designed to recapitulate human predispositions is now possible, as demonstrated by the p53 knockout mouse as a model for Li-Fraumeni syndrome (*4,23*).

• Determine the role of age in environmentally related diseases. Aging modifies the response of an individual to environmental exposures. The NIEHS, in conjunction with the National Institute of Aging and other agencies, should consider age-related factors in environmental health as an area of increasing concern and should enhance or initiate research programs in this area.

• Studies of nonmutagenic mechanisms of environmental chemicals can lead to better hazard identification and risk assessment. The paradigm for environmental causes of human diseases, particularly cancer, has been the ability of electrophilic chemicals to damage DNA and cause mutations (*24*). This paradigm is considered correct for many chemicals and should be the basis for the initial evaluation of chemical hazards as outlined above. However, nonmutagenic mechanisms are clearly important in carcinogenesis as well as other environmentally related diseases. Mechanistic studies on cell proliferation and cell death, cell–cell interaction and communication, receptor-mediated biological responses, and regulation of gene expression, among others, are important for study. Coordinated and integrated programs to apply this knowledge to carcinogen evaluation and risk assessment should be further established.

In conclusion, prevention of environmentally related diseases remains an important but unachieved public health objective. The NTP and the NIEHS can better contribute to this public health goal by encouraging multidisciplinary interactions among scientists involved in mechanistic studies, carcinogen testing, and epidemiology. Testing for potential human carcinogens can be further improved by development of mechanism-based tests to predict carcinogens using biological activity and chemical structure.We should constantly question the relevance of the testing program to humans by determining whether chemicals identified in rodents have effects in humans. For example, it is estimated that one-third of all known carcinogens were identified first as carcinogens in rodents (*25–27*). Certain human populations are known to have elevated risks to cancer (e.g., farmers), yet the exact etiological agents are unknown. Rodent carcinogen bioassays in conjunction with epidemiological studies are necessary to identify and prevent these causes of cancer. Finally, although the mutagenicity of chemicals is a clearly established mechanism of cancer induction, other mechanisms related to perturbations of signal transduction pathways remain to be elucidated. Further insights into how chemicals influence biological systems by nonmutagenic mechanisms will lead to a better understanding of the impact of environmental agents on cancer as well as noncancer endpoints.

J. Carl Barrett
Environmental Carcinogenesis Program
NIEHS

References

1. Ashby J, Tennant RW. Prediction of rodent carcinogenicity for 44 chemicals: results. Mutagenesis 9:7–15 (1994).
2. Huff J, Haseman J, Rall D. Scientific concepts, value, and significance of chemical carcinogenesis studies. Annu Rev Pharmacol Toxicol 31:621–652 (1991).
3. Ward JM, Ito N. Development of new medium-term bioassays for carcinogens. Cancer Res 48:5051–5054 (1988).
4. Jacks T, Remington L, Williams BO, Schmitt EM, Halachmi S, Bronson RT, Weinberg RA. Tumor spectrum analysis in *p53*-mutant mice. Curr Biol 4:1–7 (1994).
5. Dawe CJ. Introduction: focus and objectives of workshop on chemically contaminated aquatic food resources and human cancer risk. Environ Health Perspect 90:3–4 (1991).
6. Tsutsui T, Barrett JC. Detection of non-mutagenic carcinogens using cultured Syrian hamster embryo cells. Alt Anim Testing Exp 1:65–73 (1991).
7. Haseman JK, Huff JE. Species correlation in long-term carcinogenicity studies. Cancer Lett 37:125–132 (1987).1
8. Haseman J, Lockhart A. The relationship between use of the maximum tolerated dose and study sensitivity for detecting rodent carcinogenicity. Fundam Appl Toxicol 22:382–391 (1994).
9. Tomatis L. Transgeneration carcinogenesis: a review of the experimental and epidemiological evidence. Jpn J Cancer Res 85:443–454 (1994).
10. Huff J, Hoel D. Perspective and overview of the concepts and value of hazard identification as the initial phase of risk assessment for cancer and human health. Scand J Work Environ Health 18:83–89 (1992).
11. Rogers AE, Zeisel SH, Groopman J. Diet and carcinogenesis. Carcinogenesis 14:2205–2217 (1993).
12. Willett WC. Diet and health: what should we eat? Science 264:532–537 (1994).
13. Rao GN. Diet for Fischer-344 rats in long-term studies. Environ Health Perspect 102:314–315 (1994).
14. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 18:1–29 (1992).
15. Huff J, Boyd J, Barrett JC. Hormonal carcinogenesis and environmental influences: background and overview. In: Cellular and molecular mechanisms of hormone carcinogenesis: environmental influences (Huff J, Boyd J, Barrett JC, eds). New York:Wiley-Liss, in press.
16. McLachlan JA. Functional toxicology: a new approach to detect biologically active xenobiotics. Environ Health Perspect 101:386–387 (1993).
17. Ries LAG, Hoar Zahm S, Cheson BD. Non-Hodgkin's lymphoma. In: SEER cancer statistics review: 1973–1990 (Miller BA, Ries LAG, Hankey BF, Kosary CL, Harras A, Devesa SS, Edwards BK, eds). NIH Publication no. 93-2789. Bethesda, MD:National Cancer Institute, 1993.
18. Hoar Zahm S, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. A case–control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in Eastern Nebraska. Epidemiology 1:349–356 (1990).
19. Hoar Zahm S, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Res 52(suppl):5485–5488 (1992).
20. Hoar Zham S, Blair A. Cancer among migrant and seasonal farmworkers: an epidemiologic review and research agenda. Am J Ind Med 24:753–766 (1993).
21. Dragani TA, Manenti G, Gariboldi M, Falvella S, Pierotti MA, Della Porta G. Genetics of hepatocarcinogenesis in mouse and man. In: Oncogene and transgenics correlates of cancer risk assessments (Zervos C, ed). New York:Plenum Press, 1992;67– 80.
22. Drinkwater NR, Bennett LM. Genetic control of carcinogenesis in experimental animals. Prog Exp Tumor Res 33:1–20 (1991).
23. Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery CA, Butel JS, Bradley A. Mice deficient for *p53* are developmentally normal but susceptible to spontaneous tumours. Nature 356:215–221 (1992).
24. Miller EC, Miller JA. The presence and significance of bound aminoazo dyes in the livers of rats fed *p*-dimethylaminoazobenzene. J NIH Res 4:66–77 (1992).
25. Tomatis L. The predictive value of rodent carcinogenicity tests in the evaluation of human risks. Annu Rev Pharmacol Toxicol 19:511–530 (1979).
26. Huff J. Chemicals and cancer in humans: first evidence in experimental animals. Environ Health Perspect 100:201–210 (1993).
27. IARC. Hepatitis viruses. In: IARC monographs on the evaluation of carcinogenic risks to humans, vol 59. Lyon:International Agency for Research on Cancer, 1994;17–37.